UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/728,521	12/05/2003	Atul Varadhachary	HO-P02703US2	8270

26271 7590 06/10/2008
FULBRIGHT & JAWORSKI, LLP
1301 MCKINNEY
SUITE 5100
HOUSTON, TX 77010-3095

EXAMINER	
KAM, CHIH MIN	
ART UNIT	**PAPER NUMBER**
1656	
MAIL DATE	**DELIVERY MODE**
06/10/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/728,521
Filing Date: December 05, 2003
Appellant(s): VARADHACHARY ET AL.

Allen E. White
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed April 2, 2008 appealing from the Office action mailed July 5, 2007.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Van Bree *et al.* (WO 01/72322).

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 7, 14, 17-19, 26-32 and 38-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Van Bree *et al.* (WO 01/72322, October 4, 2001).

Van Bree *et al.* teach human lactoferrin (hLF) can block free LPS and cause them to clear from the body more rapidly, and mask their inflammatory activity; and hLF or LF variants (e.g., N-terminal variants with 1-4 arginine deleted, hLF-2N, hLF-3N, hLF-4N, hLF-5N; pages 3, 4, 5 and 27), which have the biological activities of natural LF (e.g., effective in killing viruses or bacteria; binding to high affinity LF receptors on cells), can be used to treat large scale (bacterial) infection, blood-borne infection (sepsis) as well as inflammation resulting from an infection by parenteral and/or oral administration (pages 3-4; page 20, lines 24-29; pages 24, 26; claim 1), where the concentration of the polypeptide (LF or LF variant) in the pharmaceutical composition can be at least 1% to 20% by weight (page 24, lines 10-12); and lactoferrin/variant can be administered orally in the form of a solid or solution, and the active components can be encapsulated in gelatin capsules together with inactive ingredients and carriers such as glucose,

mannitol or magnesium carbonate (an antacid; claim 14), and the formulated solid or liquid formulations can be in an enteric-coated form (page 26; claims 7, 17-19). Although the reference does not provide a specific example for a method of treating bacteremia, enhancing a mucosal immune response or decreasing mortality using a lactoferrin composition containing the N-terminal variant, it indicates a high dose of hLF and/or LF variant (e.g., N-terminal variant) having the biological activity of natural LF can be orally administered, optionally in conjunction with parenteral administration because the oral administration has advantages such that the LF can be used in a matrix without little or no purification for human consumption when the LF/variant is produced by expression in a transgenic animal (page 26, lines 1-21). Van Bree teaches a method of treating large scale (bacterial) infection, blood-borne infection (sepsis) as well as inflammation resulting from an infection (see above) by parenteral and/or oral administration of LF/variants to subjects, which has the same method step as the claimed invention, thus at the time of invention was made, it would have been obvious to one of ordinary skill in the art to orally administer N-terminal variant of LF in the method of treating bacteremia or sepsis, enhancing a mucosal immune response or decreasing mortality to produce the desired effect as the LF (claims 26-32, 38-40), which results in the claimed invention and was, as a whole, prima facie obvious at the time the claimed invention was made.

Claim Rejections-Obviousness Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 7, 14, 17-19, 26-32 and 38-40 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 16-22, 26-30 and 50-51 of copending Application No. 10/663,258 (based on the amended claims filed September 26, 2006). Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1, 7, 14, 17-19, 26-32 and 38-40 disclose a method of treating bacteremia or sepsis, enhancing a mucosal response in the gastrointestinal tract or decreasing mortality of a subject, comprising the step of administering orally to a subject an effective amount of a lactoferrin composition comprising at least 1% to at least 50% w/w of an N-terminal lactoferrin variant to provide an improvement in the condition of said subject, wherein the N-terminal lactoferrin variant has a deletion, substitution, or combination thereof, of from 1 to 16 N-terminal amino acid residues and wherein the N-terminal lactoferrin variant retains the same biological function as full length lactoferrin; and the specification indicates sepsis or bacteremia may originate anywhere in the body such as surgical wounds or decubitus ulcers (paragraphs [0003] and [0082]). This is an obvious variation in view of claims 16-22, 26-30 and 50-51 in the copending application which disclose a method of treating a wound other than ophthalmic wounds, or enhancing the local or systemic immune system in a subject suffering from a wound by administering including orally to the subject an effective amount of a lactoferrin composition, and the specification indicates a lactoferrin composition can have an N-

terminal lactoferrin variant such as N-terminal glycine deleted or substituted or a deletion, substitution, or combination thereof, of from 1 to 16 N-terminal amino acid residues and the N-terminal lactoferrin variant retains the same biological function as full length lactoferrin (paragraphs [0009] and [0048]); and the lactoferrin composition can decrease bacterial infection of the wound (paragraphs [0102]). Both the claims of instant application and the claims of the copending application are directed to a method of treating bacteremia or sepsis, or treating wounds such as wounds causing bacteremia or sepsis by administering including orally a lactoferrin composition comprising an N-terminal lactoferrin variant. Thus, claims 1, 7, 14, 17-19, 26-32 and 38-40 in present application and claims 16-22, 26-30 and 50-51 in the copending application are obvious variations of a method of treating bacteremia or sepsis, or treating wounds causing bacteremia or sepsis by administering including orally a lactoferrin composition comprising an N-terminal lactoferrin variant.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

(10) Response to Argument

In the brief, the third paragraph at page 7, Appellant indicates that the Examiner has failed to show that Appellant's claims are prima facie obvious in view of the prior art because (1) the prior art does not teach all of Appellant's claim limitations, and (2) no rationale to support an obviousness rejection is presented. In the brief, the first paragraph at page 8, Appellant indicates that the statements made by Examiner in the final Office Action regarding Van Bree's reference are not correct, they are (1) Van Bree teaches oral administration of lactoferrin ("LF") and variants thereof; (2) Van Bree teaches N-terminal LF variants having the same biological

function as natural LF; and (3) LF and N-terminal variants thereof can treat large scale (bacterial) infections, blood borne infection (sepsis), and inflammation due to infection provided the composition administered is 1-20% LF or LF variant (see p. 2-3 of Final Action).

Appellant's response has been considered but is not found persuasive because while Van Bree teaches parenteral administration of high doses of LF and LF variants to treat some conditions such as gastroenteritis, sepsis, systemic inflammation and others (page 3, lines 3-28), the reference also discloses various methods for administering pharmaceutical composition, including parenteral and oral administration (page 23, line 21-page 26). Specifically, Van Bree states that intact lactoferrin, fragments and variants can be used as pharmaceuticals and such pharmaceutical compositions are usually administered parenterally, preferably intravenously; and oral administration can also be used, optionally but not necessarily, in conjunction with parenteral administration (page 23, lines 21-26; page 26, lines 1-21). Therefore, Van Bree does teach oral administration of lactoferrin ("LF") and variants thereof. Regarding N-terminal LF variants, Van Bree indicates the N-terminal LF variants, have the biological activities of natural LF, e.g., binding to high affinity LF receptors on cells (page 3, lines 33-34; page 4, lines 13-14), regulation of cytokines (page 19, lines 12-27), and/or having antimicrobial activity (e.g., effective killing of viruses or bacteria; page 27, lines 12-14). Therefore, Van Bree teaches N-terminal LF variants having the same biological function as natural LF. Van Bree discloses high dosage parenteral administration of lactoferrin or a pharmaceutical composition containing the same can be used in a variety of therapeutic applications (page 18, lines 30-33), which include local infection, large scale (bacterial) infections, blood borne infection (sepsis), and inflammation resulting from an infection or non-infectious inflammatory diseases (page 20, lines

24-26). Further, Van Bree discloses the dosage of lactoferrin/fragment administered, the active ingredient of the pharmaceutical composition, can vary widely, usually being at least 1% by weight to as much as 20% by weight (page 23, line 25 to page 24, line 12). Therefore, Van Bree describes the use of LF and N-terminal variants thereof to treat large scale (bacterial) infections, blood borne infection (sepsis), and inflammation due to infection, where the composition administered is 1-20% LF or LF variant.

In the brief, from the second paragraph of page 8 to the paragraph bridging page 9 and page 10, Appellant argues that Van Bree does not teach oral administration without parenteral administration. Appellant indicates Van Bree describes, "methods of treating human patients by parenteral administration of relatively high dosages of lactoferrin," and "LF and fragments or variants of LF are used at high doses, with a lack of adverse side effects, to treat diseases and conditions that require a bolus of and/or sustained large doses." (see p.3, lines 3-16). Van Bree also describes indications for the administration of LF and/or LF variants, but only parenteral administration is mentioned (see p.18, lines. 31-33). After again emphasizing parenteral administration, Van Bree discloses oral administration as optionally used in conjunction with parental administration (page 23, lines 16-22; see also claims 13-15 of Van Bree). Appellant further argues that it was known in the art that LF is not systemically bioavailable when ingested; even high oral doses of LF do not significantly raise plasma LF levels (see Van Bree, p.2-3; Kuhara *et al.*, Nutrition and Cancer, Vol 28, No 2, 2000, pp. 192-199 at pg. 197, lines 8-10; EXHIBIT B). Thus, one of skill in the art would not read Van Bree and believe that oral administration could provide the same benefits of systemic LF provided parenterally in high dosages.

Appellant's response has been considered but is not found persuasive because although Van Bree teaches parenteral administration of high doses of LF and LF variants to treat conditions such as gastroenteritis, sepsis, systemic inflammation and others (page 3, lines 3-28), the reference discloses various methods for administering pharmaceutical composition, including parenteral and oral administration (page 23, line 21-page 26). Van Bree indicates pharmaceutical compositions comprising lactoferrin, fragments and variants can be administered parenterally, and oral administration can also be used, optionally but not necessarily, in conjunction with parenteral administration (page 23, lines 21-26; page 26, lines 1-21). Thus, Van Bree discloses the oral administration of LF/fragments can be used alone aside from the conjunction use of oral administration and parenteral administration of of LF/fragments. Examiner agrees that LF is not systemically bioavailable when ingested, however, Van Bree discloses LF has many biological functions (page 21, line 33 to page 23, line 18), and the ingested LF can provide some beneficial effects when administered (page 21, line 33 to page 23, line 18), e.g., inhibiting release of certain cytokines such as Il-1, Il-2 or TNF-α. This beneficial effect can also be shown by Kuhara *et al.* (Exhibit B), which discloses orally administered lactoferrin enhances production of IL-18 in the intestinal epithelium, and exerts antimetastic effect (see abstract). Since Van Bree discloses oral administration of LF/fragments in addition to parenteral administration for the treatment of many infection conditions, even high oral doses of LF do not significantly raise plasma LF levels, some beneficial effects of administered LF/fragments may be produced. Thus, one of skill in the art in reading Van Bree would believe that oral administration of LF/fragments could provide beneficial effects in the treatment.

In the brief, the second paragraph of page 10, Appellant argues that the Examiner indicates that Van Bree (at pages 4, 5, and 27) discloses N-terminal LF variants having the same biological activity *(e.g.* effective in killing virus and bacteria) of natural LF where the N-terminal amino acids 2-5 are deleted or mutated to remove the positive charge(s). However, these activities are examples of antimicrobial activity, not examples of LF functional equivalence (see p.27, lines 12-14). To compare with Van Bree, Appellant further argues certain biological and/or functional activity of an LF protein that is retained in an N-terminal LF variant is described in Appellant's Specification, which includes stimulating the production of various cytokines (e.g., IL-18, MIP-3α, GM-CSF or IFN-γ), inhibiting various cytokines (e.g., IL-2, IL-4, IL-5, IL-6, IL-10, and TNF-α), attenuating sepsis, attenuating septic shock, attenuating organ failure, decreasing morbidity, and/or decreasing mortality (see paragraphs [0046], [0060]-[0064]). Thus, the Examiner has not shown that Van Bree teaches variants with the full length LF activity that Appellants describe.

Appellant's response has been considered but is not found persuasive because Van Bree describes the full length of lactoferrin has many biological functions, and antimicrobial activity is one of them. Van Bree describes the N-terminal LF variants, like the full length of lactoferrin, have antimicrobial activity (e.g., effective killing of viruses or bacteria; page 27, lines 12-14). The variants also have binding activity to high affinity LF receptors on cells (page 3, lines 33-34), but with reduced binding, relative to natural LF, to heparin, DNA, human lysozyme, the lipid A component of bacterial lipopolysaccharide (LPS) and sulfated cell surface molecules (page 3, line 28 to page 4, line 19). Furthermore, Van Bree discloses intact LF and LF variants can reduce or inhibit release of a cytokine and have other functions (page 21, line 33 to page 23,

line 18). Thus, Van Bree discloses the N-terminal LF variant retains the same biological function (i.e., antimicrobial activity, binding to high affinity LF receptors on cells; and other functions) as the full length of lactoferrin. While the instant specification cites many functions of lactoferrin, the instant claims merely recite the N-terminal lactoferrin variant retains the same biological function as full length of lactoferrin without identifying any specific biological function.

In the brief, the paragraph bridging between page 10 and page 11, Appellant argues that Van Bree does not teach treatment of bacteremia and/or sepsis with an effective amount of orally administered LF. Van Bree discloses LF administration for therapy or prophylaxis of infection, including local, large scale, and blood borne infection, as well as inflammation resulting from infectious or non-infectious inflammatory diseases (see p.20, lines 24-27). However, there is no suggestion or teaching in Van Bree to use an effective amount of oral LF in the treatment of bacteremia or sepsis. The sole disclosure related to therapeutic oral LF administration is directed to "infections or disorders of the digestive tract" of which bacteremia and sepsis are not examples (see p.26 11. 22-24). Treatment of bacterial infection is through intravenous administration of LF at high dosages (see p.3, lines. 14-31; p.22, lines 7-12). Appellants also argue that Van Bree's working examples do not teach treatment of infection at all (see pp. 29-35).

Appellant's response has been considered but is not found persuasive because while Van Bree teaches parenteral administration of high doses of LF and LF variants to treat conditions such as local infection, large scale (bacterial) infection, blood-borne infection (sepsis), and inflammation resulting from infection (page 3, lines 3-28; page 18, lines 30-33; page 20, line 24-29), the reference also discloses various methods for administering pharmaceutical composition,

including parenteral and oral administration for the treatment (page 23, line 21-page 26). Van Bree also indicates that pharmaceutical compositions comprising lactoferrin, fragments and variants can be administered parenterally or orally, where oral administration can be used, optionally but not necessarily, in conjunction with parenteral administration (page 23, lines 21-26; page 26, lines 1-21). Thus, Van Bree discloses the oral administration of LF/fragments can be used alone in the treatment of the cited infection conditions in addition to the conjunction use of oral administration and parenteral administration of LF/fragments. Although does not provide examples for oral administration of LF/variants in an effective amount of oral LF in the treatment of bacteremia or sepsis, the reference discloses the methods of administration (e.g., parenteral and oral administration) and an effective amount of LF/variants is administered in general term (page 23, line 20-page 27, line 8). Van Bree also indicates the treatment of infections or disorders of the digestive tract is one example for oral administration of LF/fragments (page 26, lines 22-24). Thus, one of skill in the art would read Van Bree and believe that oral administration of LF/fragments could be used in the treatment of bacteremia or sepsis.

In the brief, the second and third paragraphs of page 11, Appellant argues that the sole prior art reference differs from the claimed invention in several significant ways. First, the claimed invention requires oral administration of an effective amount of LF, while Van Bree teaches oral administration for the limited purpose of supplementing the preferential method of administration: parenteral, and to have a therapeutic effect on sepsis, high close systemic LF is required, thus teaching away from oral LF administration in a therapeutically effective amount. Secondly, Van Bree teaches N-terminal variants having different biological function as full

length LF, while the claimed invention requires the same biological activity. Appellant's claims are directed to methods of treating bacteremia, sepsis, septic conditions, decreasing mortality, and/or enhancing a mucosal immune response comprising at least the step of administering orally to a subject an effective amount of a LF composition. One of skill would have no intention to modify the prior art into something closer to the claimed invention as a whole because the knowledge in the art taught such changes *(e.g.* orally administered LF) would not work. Thus, the prior art does not include all elements of the claimed invention as a whole.

Appellant's response has been considered but is not found persuasive because Van Bree while discloses the preferential method of administration is parenteral administration of LF/variants in the treatment of bacteremia or sepsis, the reference does indicate oral administration can be used, optionally but not necessarily, in conjunction with parenteral administration, and further discloses an effective amount of LF/variants administered in general term for the treatment of infections (page 23, line 20-page 27, line 8). Even high oral doses of LF do not significantly raise plasma LF levels, Van Bree discloses LF has many biological functions (page 21, line 33 to page 23, line 18), which could provide some beneficial effects when LF/variants are administered. Furthermore, Van Bree describes the N-terminal LF variants, like the full length of lactoferrin, have antimicrobial activity (page 27, lines 12-14), binding to high affinity LF receptors on cells (page 3, lines 33-34), reducing or inhibiting release of a cytokine and have other functions (page 21, line 33 to page 23, line 18). Thus, one of skill in the art in reading Van Bree would believe oral administration of LF/fragments could be used in the treatment of bacteremia or sepsis.

In the brief, the second and third paragraphs of page 12, Appellant argues that the Examiner has failed to show that Appellant's claims are *prima facie* obvious in view of the prior art because the prior art does not teach all of Applicant's claim limitations. At most, the Examiner has indicated that oral administration of LF may be advantageous because if produced by a transgenic animal *(e.g* a cow), that excretes the LF in a human consumable form *(e.g.* milk), it may be administered without extensive purification. Examiner may have intended to argue that oral administration of a pharmaceutical was a known technique or element, applied to a known or similar method or element, but each of these bases for an obviousness rejection also requires a reasonable expectation of success or outright predictable results. Considering that it was known that ingested LF is not systemically available, and in view of Van Bree's teaching regarding the requirement that LF be made systemically available in high dosages, there can be neither a reasonable expectation of success nor the necessary measure of predictability in the Examiner's advanced modification. Thus, the Examiner's burden is not met and the rejection under 103 must be reversed.

Appellant's response has been considered but is not found persuasive because Van Bree while discloses the preferential method of administration is parenteral administration of LF/variants in the treatment of bacteremia or sepsis, the reference does indicate oral administration can be used alone, and describes an effective amount of LF/variants administered in general term. Furthermore, Van Bree discloses N-terminal variants like LF have many biological functions (page 3, lines 33-34; page 21, line 33 to page 23, line 18; page 27, lines 12-14), which could provide some beneficial effects when administered (page 21, line 33 to page 23, line 18). These beneficial effects are supported by Kuhara *et al.* (2000), which describes oral

administration of lactoferrin enhances cellular immunity and exerts an antimetastatic effect. In addition, Van Bree also indicates oral administration of LF/variants may be advantageous because these peptides when obtained from transgenic animal can be administered without extensive purification. In view of foregoing response, one of skill in the art in reading Van Bree would believe that oral administration of LF/variants could provide some benefits in treating bacteremia or sepsis.

In the brief, from page 14 to page 15, Appellant indicates since the cited co-pending application (10/663,258) has not issued, and currently remains in prosecution, it is proper for the Board to address the merits of Appellant's arguments above and withhold opinion as to the double patenting rejection without finding Appellant concedes to the propriety of the rejection as *Appellant explicitly does not concede.* Appellant has acknowledged the provisional double-patenting rejections, and the Examiner has noted this acknowledgement. Appellant further indicates that Appellant is not required to address the merits of the provisional double-patenting rejections until such time as the co-pending application(s) issue and the rejections are made non-provisional.

Appellant's response has been considered. M.P.E.P. § 804 indicates that while a provisional double-patenting rejection is pending, prosecution, including appeal, should continue, and the Office may continue to make such a provisional rejection until one of the applications issues as a patent. In view of the remaining rejection, the provisional double-patenting rejection is maintained.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Chih-Min Kam/

Chih-Min Kam

Primary Examiner

Art Unit 1656

Conferees:

/Kathleen Kerr Bragdon/
Kathleen Kerr Bragdon
Supervisory Patent Examiner
Art Unit 1656

Deleted: /Robert A. Wax/¶
Robert A. Wax¶
TQAS Appeals Specialist¶
Technology Center 1600¶
¶
¶
¶
¶

/Robert A. Wax/
Robert A. Wax
TQAS Appeals Specialist
Technology Center 1600

Deleted: ¶